IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Confirmation No.: 6533

Aurelio Orjales Venereo, *et al.*

Serial No.: 10/511,822 Group Art Unit: 1625

Filed: March 23, 2005 Examiner: Celia C. Chang

For: POLYMORPH OF 4-[2-[4-[1-(2-ETHOXY)-1H-BENZIMIDAZOLE-2-YL]-1-PIPERIDINYL]ETHYL]-αα-DIMETHYL-BENZENEACETIC ACID

VIA EFS-WEB
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

1. I, Maria Luisa Lucero de Pablo, am a Spanish citizen, residing at Basarrate, 26 1° izda., E-48990, Algorta, Spain. I am a co-inventor of the above-identified U.S. patent application. As detailed below, I am employed by Faes Farma, S.A., the owner by Assignment of the above-identified application. I have read and am familiar with the U.S. Patent Office Action dated January 9, 2009 concerning the subject application. I understand that among the rejections cited in the Office Action, the Examiner rejected claim 35 on the basis that the claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as recited in the claim. I am making this declaration to support the patentability of the claims of the above-identified application.

2. A copy of my *curriculum vitae* ("CV") is provided as attachment A to this declaration. My relevant educational experience is set forth under the heading "Educational Background" on p. 1 of my CV. See also the listing of training courses and Scientific Meetings, i.e., Congresses, I have attended at pp. 4-7 and 7-11, respectively, of my CV. My relevant employment experience, including details of my employment with Faes Farma, S.A., the Assignee of the present application, are as set forth under the heading

"Occupational Experience" on p. 2 thereof. See also the list of drugs and compounds I have investigated under the heading "Investigation Lines" on pp. 3-4 of my CV. My list of Publications is found at p.12, whereas a list of patents/applications on which I am an inventor/co-inventor is found at p. 13. The scientific associations to which I belong are set forth on p. 12. I submit that, in accordance with the details provided in my CV, I am one having at least ordinary skill in the field of the compositions and methods recited in the claims of the present application.

3. According to the Office Action (¶3, p. 2), in order for a patent specification to meet the enablement requirement, an invention must be described therein so that any person skilled in the art can made and use the invention without undue experimentation. The rejected claim, i.e., claim 35, is directed to an antihistiminic pharmaceutical composition comprising a novel and unobvious crystalline form 1 of bilastine as an active ingredient (the active ingredient is recited in claim 25 which has been found allowable by the Examiner), together with at least one excipient. The Examiner submits, on p. 3 of the Office Action, however, that the temperature and pressure involved in the processing steps used to form the claimed pharmaceutical composition would cause transformation of bilastine form 1 into one or more different polymorphic forms. That is, the Examiner takes the position that the temperature and pressure used in forming the claimed composition (recited in claim 35) would cause the particularly claimed "Form 1" of bilastine to convert to one of the other polymeric forms (i.e., form 2 and/or form 3) of bilastine. The Examiner concludes, at the bottom of p. 3 in the Office Action, that applicants did not provide any evidence in the specification of the application that the crystalline drug would keep its form, i.e., would remain in 'Form 1' in the pharmaceutical composition, i.e., as recited in claim 35.

4. I respectfully disagree with the Examiner's conclusion that, as indicated above, the form 1 of bilastine would be converted to another form. I submit that the evidence described below conclusively demonstrates that the crystalline 'Form 1' of bilastine would, in fact, maintain its form in a pharmaceutical composition according to claim 35, i.e., notwithstanding the temperature(s) and pressure(s) encountered in the methodology used in forming the composition.

5. As indicated in the present specification (see, e.g. paragraphs [0013] and [0021] of the published U.S. patent application, No. 2005/0203141 A1) among the three different polymorph forms of bilastine, crystalline form 1 is the most stable. This new polymorph form is obtained from the polymorphs 2 and 3 by crystallization, upon heating under reflux conditions in isopropyl alcohol (20 min at ≈ 83 °C), n-butanol (3 hours @ ≈ 117 °C) or acetone (several hours at ≈ 56 °C). The Examiner's attention is respectfully directed to the fact that under the indicated conditions, no reversion to either polymorph 2 or polymorph 3 takes place (see paragraph [0021] of US 2005/0203141 A1). This clearly demonstrates the higher thermodynamic stability of the claimed crystalline form 1 over the Forms 2 and 3 which were previously known in the prior art. Further, the teachings serve to enable the use of bilastine Form 1 as an active ingredient of a pharmaceutical preparation as described in paragraph [0022] of the published application, i.e., in that bilastine form 1 can be counted on not to convert into another form due to the processing conditions encountered. Polymorph 1 of bilastine is stable even when stored at room temperature and above, as described in the present application. Therefore, there is no reason to believe that bilastine in crystalline form 1 does not keep its form in the solid pharmaceutical composition recited in claim 35, notwithstanding the temperature and pressure encountered during the formation of the claimed composition.

6. In my view as one skilled in this art, the specification discloses solid pharmaceutical compositions of crystalline form 1 of bilastine in a manner sufficiently clear and complete for them to be prepared and incorporated into the claimed pharmaceutical composition by an individual having ordinary skill in this field of art without any undue experimentation, since bilastine in crystalline form 1 is sufficiently stable to allow the preparation of solid pharmaceutical compositions, i.e., as recited in claim 35, without alteration to its crystalline form.

7. By me or under my direction and control a series of experiments was carried out to demonstrate the stability of crystalline form 1 of bilastine during the procedure for pharmaceutical preparation, i.e., of a composition according to claim 35. As set forth below, the experimental results achieved serve to demonstrate that, notwithstanding the Examiner's theory regarding the conversion of the bilastine from one form to another, the crystalline form 1 of bilastine remains stable during the formation of a pharmaceutical

composition according to claim 35. The form does not change or convert to any other form of bilastine, notwithstanding the pressures and temperatures encountered by the bilastine during formation of the pharmaceutical composition.

8. The polymorph 1 (crystalline form 1) of bilastine was studied in various mixtures with several excipients. The physical compatibility of the mixtures was assessed by Differential Scanning Calorimetry ("DSC") analysis, a technique that provides a rapid evaluation of possible interactions between formulation components. The DSC technique takes into account the possibility that endothermic or exothermic peaks may appear, move or disappear and/or that there may be variations in enthalpy values, by comparing thermal curves of the pure substance against those obtained with the mixtures. This study of bilastine-excipients compatibility by DSC included commonly encountered excipients as well as a tablet formulation composed of microcrystalline cellulose (diluent), sodium carboxymethyl starch (disintegrant), colloidal silicon dioxide (glidant) and magnesium stearate (lubricant). The study included DSC curves for bilastine as well as for each pure excipient that were compared with their mixtures in different proportions. In addition, the mixtures were thermally studied once pressed, as it was believed that high pressures used for pressing could cause interactions that would not occur during mere mixing. The results of this compatibility study are summarized in Table 1 provided as Attachment B to this declaration.

9. Next, a preformulation study with crystalline form 1 was conducted to obtain an immediate-release tablet formulation to be used for Phase I, Phase II and Phase III clinical studies. Compressibility studies (i.e., testing and comparing flowability, angle of repose, Carr and Hausner indexes and percent compressibility) were conducted with mixtures of different doses of the active ingredient and excipients to optimize the process for preparation of samples for clinical trials (see Table 2, Attachment C to this declaration). The results obtained clearly demonstrate that variability in the crystalline form between the various batches (mixtures) is very low and acceptable.

10. Tables 3-4 (Attachments D-E to this declaration) provide photostability data to permit a comparison between crystalline form 1 and the mixture of polymorphs 2 and 3. According to the data in Tables 3 and 4, the mixture of polymorphs 2 and 3 is chemically and thermically unstable after 15 days under irradiation by visible A and B light (see

Figure 2, Attachment G to this declaration). In contrast, new crystalline form 1 is stable against light irradiation even after 30 days (compare with Tables 3 and 4 and Figure 1, Attachment F). In the photostability study of polymorph 1, no significant degradation impurities or changes in DSC were observed in transparent or amber glass containers or in the product directly exposed to light.

11. In addition, stability data obtained under stress conditions (see Tables 5 and 6 provided as Attachments H and I to this declaration) demonstrate that polymorph 1 is completely stable against temperature and humidity in multiple stability studies whereas the mixture of polymorphs 2 and 3 demonstrates a slight degree of hygroscopicity, which complicates the pharmaceutical process.

12. From the experimental data provided herein, I conclude that polymorph 1 of bilastine demonstrates remarkable stability and would not convert to another form due to the temperature and/or pressure encountered during pharmaceutical formulation. As such the teachings contained in the present application are sufficient to enable a person having ordinary skill in the relevant art to formulate the solid pharmaceutical preparation recited in claim 35 without the need for any undue experimentation.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: April 3, 2009 By: _____

Maria Luisa Lucero de Pablo

ATTACHMENT A

MARÍA LUISA LUCERO
16/12/1949, Madrid (Spain)

R&D and Innovation
FAES FARMA, S. A.
tel: + (34) 94 481 83 00
e-mail: mlucero@faes.es

1. EDUCATIONAL BACKGROUND

- Bachelor of Industrial Technical Engineering (Process Control and Chemistry Premises). Escuela de Ingeniería Técnica Industrial, Madrid 30/October/1969. Validated on 27 September 1995 as "European Engineer" by FEANI.

- Bachelor of Pharmacy. Universidad Complutense, Madrid June/1980.

- Bachelor of Pharmacy Degree awarded (A mark) after presentation of "Estudio de la interacción de Procodazol y su ester etílico con seroalbúmina humana", June/1983.

- Graduate of Statistical Methods in Health Sciences (A mark). Mathematical Psicology Department, Universidad Autónoma de Barcelona, 6/July/1987.

- Qualified supervisor of 3rd category radioactive premises, jointly issued by the Instituto de Formación Científica y Tecnológica and the Consejo de Seguridad Nuclear, June/1990.

- Qualified supervisor of 3rd category radioactive premises for "Pharmacological research with non encapsulated radioisotopes" (N°IR-1776-S-2) issued by C.S.N., May/1992. Renewed every 2 years.

- Graduate of "Publications: Writing and Review" (B mark). Universidad Autónoma de Barcelona, 30/June/1995.

- Specialist pharmacist in "Industrial Pharmacy and Pharmaceutical Technology". Ministerio de Educación Cultura y Deporte, 27/October/2000.

- Specialist pharmacist in "Analysis and Control of Medicines and Drugs". Ministerio de Educación Cultura y Deporte, 7/November/2002.

2. LANGUAGES

- **English**
  Speaking: intermediate
  Reading: advanced
- **French**
  Reading: advanced

3. COMPUTER SKILLS

- Internet PC software tools such as: spreadsheets (Lotus, Excel), pharmacokinetic and statistical calculations (Stat, WinNONLIN, RSTRIP, PKAnalyst and SIPHAR), chromatography (Empower, Millenium and Access-Chrom), Office tools (WordPerfect, Word, Excel, Lotus databases).

4. OCCUPATIONAL EXPERIENCE

1970 - 1984 Head of Chemical Analysis Section, Alonga Research Centre – Pharmaceutical Laboratories *Lafarquim S.A.*

1985 - 2006 **1**. Setting-up of Analytical Chemistry and Pharmacokinetics & Metabolism areas in *FAES FARMA, S.A.*
2. Researcher in the Pharmacokinetics area and later on Head of Area.
3. Coordinator of "Pharmaceutical Technology", "Analytical Chemistry" and "Pharmacokinetics & Metabolism" areas.
4. From 1992 Head of Biopharmacy and Pharmaceutical Technology Section, including the areas mentioned above.

2006 - 2008 Deputy Directors of Research and Head of Biopharmacy and Pharmaceutical Technology Section.

2008 - ... Director of R&D and Innovation.

Collaboration with public institutions

- **Hired by the Basque Government** to participate in the Basic Curricular Design of "Quality Control in the Pharmaceutical Industry" and "Dosage and packaging of pharmaceutical products" modules corresponding to Training Cycles of "Manufacture of pharmaceutical and related products" and "Operations for Manufacture of Pharmaceutical Products" (Ley Orgánica 1/1990 del 3 de Octubre, de Ordenación General del Sistema Educativo).

5. INVESTIGATION LINES

β-lactamic antibiotics
Analytical development of 6-APA and 7-ACA and related substances
Lafarquím S.A. (Alonga). Madrid.

Unspecific stimulators of body defenses
Analytical development of benzimidazol derivatives (procodazol and tetrazol)
Lafarquím S.A. (Alonga). Madrid.

Azetidinic antibacterial derivatives
Analytical development and purity profile
Lafarquím S.A. (Alonga). Madrid.

Aminobenzoic anaphilaxis preventing derivatives
Analytical development
Lafarquím S.A. (Alonga). Madrid.

Captopril
Analytical development, stability and purity profile
Lafarquím S.A. (Alonga). Madrid.

Quinazolinone derivatives with pharmacological interest
Analytical development, stability and purity profile
Lafarquím S.A. (Alonga). Madrid.

Anti-inflammatory drugs (flufenamic acid derivatives).
Analytical development, stability and purity profile
Lafarquím S.A. (Alonga). Madrid.

Binding to plasma proteins of anti-allergic drugs
Universidad Complutense de Madrid. Facultad de Farmacia.

Anti-inflammatory drugs (Diclofenac and derivatives)
Bioavailability and bioequivalence of pharmaceutical formulations for oral, rectal and topical administration.
FAES FARMA, S.A., Research Department.

Presystemic metabolism of drugs
FAES FARMA, S.A., Research Department.

Antihistamic drugs (Pyperidine alcanamines)
Pharmacokinetics, analysis, stability.
FAES FARMA, S.A., Research Department.

Broncodilators (Fenspiride, Teophiline)
Pharmacokinetics, analysis, stability.
FAES FARMA, S.A., Research Department.

$5HT_3$ antagonists (Antiemetic, sedative drugs)

Pharmacokinetics, analysis, stability.
FAES FARMA, S.A., Research Department.

Anti-allergic drugs
Analytical and pharmaceutical development; pharmacokinetics and metabolism.
FAES FARMA, S.A., Research Department.

Antidepressants
Analytical and pharmaceutical development; pharmacokinetics and metabolism.
FAES FARMA, S.A., Research Department.

Molecules with COX-2 inhibition action.
ADME studies.
FAES FARMA, S.A., Research Department.

Molecules with action on Osteoporosis.
ADME studies.
FAES FARMA, S.A., Research Department.

6. TRAINING AND CONGRESSES

Relevant training courses:

- Intensive training on *Quantitative Applications of Atomic Absorption (AA) and Molecular (UV-VIS, IR) Spectrophotometries.* Instituto Químico de Sarria, Barcelona May/1974.
- Intensive training on *Gas Chromatography.* Instituto Químico de Sarria, Barcelona June/1975
- *High Performance Liquid Chromatography.* Waters October/1982
- *Drug Stability.* Colegio Oficial de Farmacéuticos, Madrid January/1984
- *Introduction to Selective Electrodes.* Orion Research, Madrid May/1984
- Training on *High Performance Liquid Chromatography.* Millipore/Waters, Bilbao January/1986
- *Pharmacokinetics. Basic concepts and computer-assisted development.* Institut Municipal d'Investigació Médica/IMAS, Barcelona November/1987
- *VAX/VMS general users.* Digital, Bilbao September/1989
- *VMS System Responsible.* Sociedad de Servicios e Ingeniería informática (Ibermática, S.A), Bilbao February/1992
- *Medicines and Drugs in Biological Fluids.* Institut Municipal d'Investigació Médica/IMAS, Barcelona May/1993

- Seminar on *Thermal Analysis.* Mettler, Bilbao en May/1995
- *Impurities in pharmaceutical products. International rules for tolerance.* Universitat de Barcelona/Fundació Bosch i Gimpera, Barcelona October/1996
- *Setting Specifications for Drug Substances and Drug products.* The Center for Professional Advancement, FAES January/2000
- *Analysis of the Pharmacological Effect "in vivo": Pharmacokinetic-Pharmacodynamic Relations.* Universidad del País Vasco, Facultad de Medicina, Leioa September /2000
- *Risks in Chemistry Laboratories.* Mutua Vizcaya Industrial, FAES June /2001
- *Critical Process Cleaning and Cleaning Validation.* The Center for Professional Advancement, Madrid June/2001
- *Professional improvement on GMP.* C.E.S.I.F, FAES January/2002
- *Handling Biological Agents: Prevention.* Mutua Vizcaya Industrial, FAES May/2002
- *Pharmacokinetic-Pharmocodynamic analysis: theory and practice.* Pharmadatum, FAES September/2002
- *EU-GMP and FDA Compliance in Pharmaceutical Development.* ECA, Madrid October/2002
- *Technical Review of Batch Documents.* AULA GMP, FAES November/2002
- *Risk and emergencies management in the Biopharmacy and Pharmaceutical Technology Section.* Mutua Vizcaya Industrial, FAES May/2003
- *Introduction to GLP. Recording original data.* Internal training provided by the QAU, FAES July/2003
- *II practical training on population pharmacokinetic analysis: NONMEM.* Universidad del País Vasco, Facultad de Medicina Leioa November/2003
- *Investigation of OOS Results.* AULA GMP Consulting, FAES December/2003
- *GMP´s in the Quality Control laboratory.* AULA GMP Consulting, FAES December/2003
- *GMP´s for the qualification of laboratory equipment.* AULA GMP Consulting en FAES FARMA Febrero /2004
- *Using and keeping standard reference substances and reagents.* AULA GMP Consulting, FAES February/2004
- *Meeting of advanced users of CDS2004 Chromatography.* Waters, Edinburgh

February/2004

- *Laboratory work under GLP requirements*. Aula Científica S.L., Barcelona March/2004

- *Project planning and management with Microsoft Project 2003*. RM consulting, FAES June/2004

- Seminar on *How to design and analyze bioequivalence studies successfully*. IIR, Madrid February/2005

- *European Technology Seminar*. Waters, Boston (Massachusetts) May/2005

- *Analytical method validation with ELSA software*. Waters Cromatografía, FAES June/2005

- *Creating, revising and approving master documents*. AULA GMP Consulting, FAES July/2005

- *Impurities Impurities*. Management Forum, Barcelona March/2005

- *Validation of Computer Systems under GXP*. TDV, FAES February and November/2007

- *RS/APQ Open Forum on Clinical Trial Materials – Clinical and CMC Challenges for Successful Conduct of Multi-Regional Clinical Trials*. AAPS Annual Meeting and Exposition, San Diego November/2007

- *ADMET: Creating Optimized Drug Candidates from Active Molecules*. Select Biosciences, Stockholm February/2008.

- *ADME, PK, TK and Drug Metabolism in Drug Discovery and Development*. Mondial Research, Brussels March/2008.

- *Predicting Drug Absorption: A Mechanistic Approach Based on Gastrointestinal Disposition*. ISSX, Vienna May/2008.

- *Genotoxic impurities*. Informa Life Sciences, Brussels June/2008.

- *Characterizing & communicating uncertainty in exposure assessment*. EUROTOX (WHO/IPCS), Rodhes October/2008.

Congress attendance:

Communications:

- *"Evaluación de AL-226, una nueva cefalosporina semisintética"*. C. Fuentes, I. Fernández, M.L. Lucero y M. Izquierdo. VI Congreso Nacional de Microbiología. Santiago de Compostela (1977)

- *"Synthesis and antibacterial activity of trisubstituted azetidin-2 ones"*. I. Fernández, C. Fuentes, M. Izquierdo y M.L. Lucero. VII International Symposium on Medicinal Chemistry. Torremolinos (1980)

- *"Synthesis and antianaphylactic activity of new aminobenzoic acid derivatives"*. I. Fernández, C. Fuentes, M. Izquierdo y M.L. Lucero. VII International Symposium on Medicinal Chemistry. Torremolinos (1980)

- *"Synthesis and absorption studies of 7-mandelamido-3 methyl cephalosporonates"*. I. Fernández, C. Fuentes, M. Izquierdo y M.L. Lucero. VII International Symposium on Medicinal Chemistry. Torremolinos (1980)

- *"Interacción de procodazol y su ester etílico con seroalbúmina humana"*. M.L. Lucero, I. Cayre y C. Sáiz. III Congreso Internacional de Química Terapéutica. Pamplona (1983)

- *"Metabolismo presistémico: importancia y metodología"*. M.L. Lucero. I Jornadas monográficas de la Sociedad Española de Química Terapéutica sobre Metabolismo de Fármacos. Pamplona (1992)

- *"Semi-automated solid phase extraction procedure for the high-performance liquid chromatographic determination of Alinastine in biological fluids"*. E. Corta, A. Bakkali, L.A. Berrueta, B. Gallo, F. Vicente, A. Gonzalo, M.L. Lucero and A. Orjales. 22nd International Symposium on Chromatography. Rome (1998)

- *"Matrix solid-phase dispersion technique for the determination of a new antiallergic drug in rat faeces"*. L.A. Berrueta, M. Fernandez-Armentia, A. Bakkali, A. Gonzalo, M.L. Lucero and A. Orjales.. XXIX Reunión Científica del Grupo de Cromatografia y Técnicas Afines. Alcalá de Henares (2000)

- *"Percutaneous absorption of Lerisetron in the rat"*. Ortega F, Jaureguizar N, Calvo R, Lucero ML, Orjales A., Lukas J.C. XXIII Congress of the Spanish Society of Pharmacology. Alicante (2000)

- *"Pharmacokinetics and Metabolism of the Anti-emetic Lerisetron in Man"*. S. Mayhew, B.A. John, G. Ford, M. L. Lucero and A. Orjales., 18TH European Workshop on Drug Metabolism. Valence (2002)

- *"Metabolism Pattern Characteristics of Lerisetron in Rats"*. Ortega F, Calvo R, Lucero ML, Gonzalo, A., Orjales A., and Quintana, A. XXIV Congress of the Spanish Society of Pharmacology, Toledo (2002) Poster (P60). Publicado en Methods & Findings Vol.24, Supl. A, p 118 (2002)

- *"Analysis of a Parent-Metabolite Pharmacokinetic Model for Lerisetron in Rats"*. Ortega F, Calvo R, de la Fuente L, Jaureguizar N, Lucero ML, Gonzalo, A., Orjales A., XXV Congress of the Spanish Society of Pharmacology, Cadiz (2003) Poster (P123). Publicado en Methods & Findings Vol.25, Supl. A, p 171 (2003)

- *"Clasificación de Bilastina dentro del sistema de clasificación biofarmacéutica SCB"*. Haydee Blanco, Ana Alejandro, Lourdes Sainz, Mª Luisa Lucero y Aurelio Orjales.. XIII Congreso Nacional de la Sociedad Española de Química Terapéutica. Santiago de Compostela (2003). Poster P-73

- *"Metabolismo intestinal de Bilastina. Estudio in-vitro"*. Ana Alejandro, Lourdes Sainz, Mª Luisa Lucero y Aurelio Orjales. XIII Congreso Nacional de la Sociedad Española de Química Terapéutica. Santiago de Compostela (2003). Poster P-74

- *"Determination of Bilastine in Urine by Column Switching high performanc Liquid Chromatographic Technique"*. Gonzalo A, Lucero M.L y Orjales A. 4° Congreso de la Sociedad Española de Cromatografía y Técnicas afines (SECYTA). Madrid (2004).

- *"Validation of a High-Performance Liquid Chromatography Method Using Diode-Array Detection for Dosmalfate and Related Impurities"*. Rosa Urzay, Manuel Chacón, Mª Luisa Lucero y Aurelio Orjales. 4° Congreso de la Sociedad Española de Cromatografía y Técnicas afines (SECYTA). Madrid (2004)

- *"Estudio del polimorfismo en Lerisetrón clorhidrato mediante Calorimetría diferencial de barrido (DSC)"*. Blanco Fuente Haydeé, Lucero de Pablo Mª Luisa y Orjales Venero Aurelio. XXIV Symposium de AEFI. Cordova (2004)

- *"ADME en la selección primaria de fármaco: Aplicación en compuestos inhibidores COX-2"*. Mónica Betanzos, Ana Alejandro, Haydeé Blanco, Edurne Corta, Mª Luisa Lucero y Aurelio Orjales. XIV Congreso Nacional de la Sociedad Española de Química Terapéutica. Bilbao (2005). Poster C-60

- *"Influencia de la P-glicoproteína en la farmacocinética del compuesto F-98214-TA en la rata"*. Nerea Leal, Mónica Rodríguez, Fátima Ortega, Alvaro Ganza, Mª Luisa Lucero y Aurelio Orjales. XIV Congreso Nacional de la Sociedad Española de Química Terapéutica. Bilbao (2005). Poster C-85

- *"Metabolismo presistémico del F-91506-RR en ratas Wistar hembra y macho"*. Ana Gonzalo, Mª Luisa Lucero y Aurelio Orjales. XIV Congreso Nacional de la Sociedad Española de Química Terapéutica. Bilbao (2005). Poster C-61.

- *"Aplicación de la dispersión en fase sólida para la determinación de nuevas drogas farmacéuticas en cerebro de rata"*. L.A. Berrueta, M.B. Sánchez, I. Crespo-Ferrer, B. Gallo, F. Vicente, M. L. Lucero y A. Orjales. XIV Congreso Nacional de la Sociedad Española de Química Terapéutica. Bilbao (2005). Poster C-94.

- *"Effect of F-98214-TA3 and Other Antidepressants in the Learned Helplessness Model"*. I. Artaiz, A. Zazpe, L. Labeaga, M. Lucero, A. Pazos, A. Orjales. 36th Annual Meeting, Society for Neuroscience. Atlanta, Georgia (2006). Poster 287.6.

- *"Fijación a proteínas plasmáticas en diferentes especies de F-98214-TA, un nuevo inhibidor de la recaptación de serotonina y noradrenalina"*. I. Soangas, F. Ortega, A. Ganza, M. L. Lucero, A. Orjales, R. Calvo. 28 Congreso Nacional de la Sociedad Española de Farmacología, Santiago de Compostela (2006). Poster 157.

- *"In vitro hepatic metabolism of [^{14}C]-Bilastine"*. M. L. Lucero, A. Orjales, N. Morag. 8th International ISSX Meeting, Sendai (2007). Poster 160.

- *"The disposition, metabolism and elimination in rats of Bilastine, a potent, selective H_1 receptor antagonist"*. R. Mumford, L. Allan, R. Hoey, A. Patterson, M. L. Lucero, A. Orjales, C. Crean. 8th International ISSX Meeting, Sendai (2007). Poster 282.

- "*Preclinical Pharmacokinetics of Bilastine, a new antihistamine drug, in rats and dogs*". A. Gonzalo, M. Lucero, A. Orjales. AAPS Annual Meeting and Exposition, San Diego (2007). Poster 2867.

- "*Validated HPLC method for analysis of bilastine in plasma from mouse, rat, dog and rabbit*". A. Ganza, A. Gonzalo, M. L. Lucero, A. Orjales. AAPS Annual Meeting and Exposition, San Diego (2007). Poster 2877.

- "*Compatibility study between bilastine and tablet excipients using differential scanning calorimetry (DSC)*". H. Blanco, M. Lucero, A.Orjales. AAPS Annual Meeting and Exposition, San Diego (2007). Poster 2860.

- "*Benzylpiperidin-4-yl-amines: an exploration into the field of antidepressants with dual action on neurokinin-1 receptor and serotonin transporter*". A. Orjales, M. L. Lucero, R. Mosquera, L. Alonso, L. Labeaga, A. Innerárity, R. Corcóstegui, Roberto Olivera. European Federation for Medicinal Chemistry, Slovenia (2007).

- *"Synthesis and biological evaluation of newthiazole derivatives"*. A. Orjales, M. L. Lucero, Ramón Mosquera, Luis Labeaga, Mª Teresa Nuñez, Víctor Rubio, Rosa Rodes. European Federation for Medicinal Chemistry, Slovenia (2007).

- "*New 2-aminoethanol derivatives as orally active antiestrogenic agents*". A. Orjales, M.L. Lucero, R. Mosquera, L. Labeaga, A. Berisa, I. Tapia, N. García-Domínguez, P. López-Tudanca, R. Rodes. European Federation for Medicinal Chemistry, Slovenia (2007).

- "*Modelado farmacocinético poblacional de Bilastina, un nuevo antihistamínico H_1, en rata*". I. Ortega, a. Gonzalo, R. Calvo, M. L. Lucero, A. Orjales. 1ª Jornada de Nacional de Modelización y Simulación en Biomedicina, Valence (2007).

- "*Early identification of the processes involved in Bilastine bioavailability in rats*". A. Gonzalo, N. Leal, M. L. Lucero, A. Orjales, M. Rodríguez. 10th European ISSX Meeting ,Vienna (2008).

- "*Early identification of the processes involved in Bilastine bioavailability in rats*". A. Gonzalo, N. Leal, M.L. Lucero, A. Orjales, M. Rodríguez. 10th European ISSX Meeting, Vienna (2008).

- *"Differential involvement of central and peripheral mechanisms in the suppressant effect of duloxetine on formalin-induced pain behaviors in rats"*. I. Artaiz; A. Zazpe; F. Ledo; A. Orjales; M.L. Lucero. 6th Forum of European Neuroscience (FENS), Ginebra (2008). Poster D50.

- *"PEG-coated nanoemulsions, a carrier of pharmaceutical interest for the delivery of antitumoural drugs"*. P. Hervella, M. Alonso-Sande, M. García-Fuentes, F. Ledo, M.L. Lucero, M. J. Alonso. 35th Annual Meeting and Exposition of the Controlled Release Society, New York (2008). Poster 922.

- *"Estimation of Bilastine dose in children"*. M. Rodríguez, M.L. Lucero, A. Orjales, A. Gonzalo, N. Leal, R. Calvo. The 9th World Congress on Clinical Pharmacology and Therapeutics (CPT), Quebec (2008).

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8. PATENTS

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9. SCIENTIFIC ASSOCIATION

- Funding member of the *Sociedad de Química Terapéutica*
- Member of the *Real Sociedad de Química*
- Member of *AEFI (Asociación Española de Farmacéuticos de Industria)*
- Member of the *Sociedad de Cromatografía y Técnicas Afines*
- Member of the *International Society for the Study of Xenobiotics (ISSX)*
- Member of the *American Association of Pharmaceutical Scientists (AAPS)*

ATTACHMENT B

Table 1: Compatibility Bilastine (polymorph 1): Excipients

Bilastine : Excipient	**Mixture (w:w)**	**Compatibility/Incompatibility**
Bilastine : Microcrystalline cellulose	(1:1)	Compatible
Bilastine : Lactose monohydrate	(1:1)	Compatible
Bilastine : Sodium carboxymethyl starch	(1:1) (1:0.5) (1:0.25)	Compatible
Bilastine : Croscarmellose sodium	(1:1)	Compatible
Bilastine : Coloidal silicon dioxide	(1:1) (1:0.5) (1:0.25)	Compatible
Bilastine :Talc	(1:1)	Compatible
Bilastine : Dihydrate sodium sacharine	(1:1) (1:0.5) (1:0.25)	Compatible
Bilastine: Excipients mixture like as tablet composition	Tablet	Compatible

ATTACHMENT C

Table 2: Flowability and compressibility study of Polymorph 1

	Batch (Mixture)			
	E31/01/D0	**E31/01/D10**	**E31/01/D20**	**E31/01/D30**
Bulk density (g/cm^3)	0.390	0.392	0.387	0.384
Tapped density (g/ml)	0.476	0.478	0.474	0.486
Bulk volume (ml)	100	100	100	100
Tapped volume (ml)	82	82	81.5	79
IC (Carr Index) %	18.0	18.0	18.5	21.0
IH (Hausner Index)	1.22	1.22	1.23	1.27
% C (Compressibility in percent)	12.8	13.2	11.8	16.1
$V_{10} - V_{500}$ (ml)	12.0	12.5	11.0	15.0

D = doses (10, 20, 30 mg)

ATTACHMENT D

Table 3: **Photostability study with Polymorph 1**

Study code	Batch	Packaging	Conditions	Duration
EST-01/03	4002J40 4202J41-2	Transp glass bottle Amber glass bottle Petri dish without cover	12000 LUX	30 days

ATTACHMENT E

Table 4: Study EST-01/03: Photostability study: Batches 40002J40 and 4202J41-2

Conditions Container	Storage time	Appearance	Assay (%)	Moisture (%)	Impurities (%)						DSC	
					F-98226-BM	F-97614-BM	F-90021-RR	F-97617-BM	UID	Total (ID + UID)	Polymorph	Onset Temp. (°C)
Specifications		White or off-white powder	97.5-101.5 %	≤0.5 %	≤0.7 %	≤0.2 %	≤0.4 %	≤0.2 %	≤0.1 %	≤1.5 %	Corresponds to Polymorph I	
Batch 4002J40 (Batch size: 17.65 kg; Date of manuf: Oct 02; FAES FARMA)												
-	Initial	Conforms	99.0	0.1	0.38	ND	0.21	ND	<QL	0.59	I	199.16
12000 LUX	15 days	Conforms	98.7	0.1	0.38	ND	0.21	ND	<QL	0.59	I	199.05
Transparent glass bottle	30 days	Conforms	99.5	0.2	0.38	ND	0.22	ND	<QL	0.60	I	199.04
12000 LUX	15 days	Conforms	98.8	0.1	0.38	ND	0.21	ND	<QL	0.59	I	199.03
Amber glass bottle	30 days	Conforms	99.3	0.2	0.37	ND	0.22	ND	<QL	0.59	I	199.12
12000 LUX	15 days	Conforms	98.5	0.2	0.39	ND	0.20	ND	<QL	0.59	I	198.67
PP Petri dish without cover	30 days	Conforms	98.6	0.2	0.39	ND	0.20	ND	<QL	0.59	I	198.51
Batch 4202J41-2 (Batch size: 17.10 kg; Date of manuf.: Oct 02; FAES FARMA)												
-	Initial	Conforms	98.8	0.1	0.32	ND	0.18	ND	<QL	0.50	I	199.33
12000 LUX	15 days	Conforms	98.7	0.1	0.32	ND	0.17	ND	<QL	0.49	I	199.29
Transparent glass bottle	30 days	Conforms	99.1	0.2	0.32	ND	0.17	ND	<QL	0.49	I	199.32
12000 LUX	15 days	Conforms	99.0	0.1	0.32	ND	0.17	ND	<QL	0.49	I	199.36
Amber glass bottle	30 days	Conforms	99.3	0.2	0.31	ND	0.18	ND	<QL	0.49	I	199.37
12000 LUX	15 days	Conforms	98.4	0.1	0.33	ND	0.16	ND	<QL	0.49	I	198.92
PP Petri dish without cover	30 days	Conforms	98.2	0.2	0.32	ND	0.16	ND	<QL	0.48	I	198.64

ATTACHMENT F

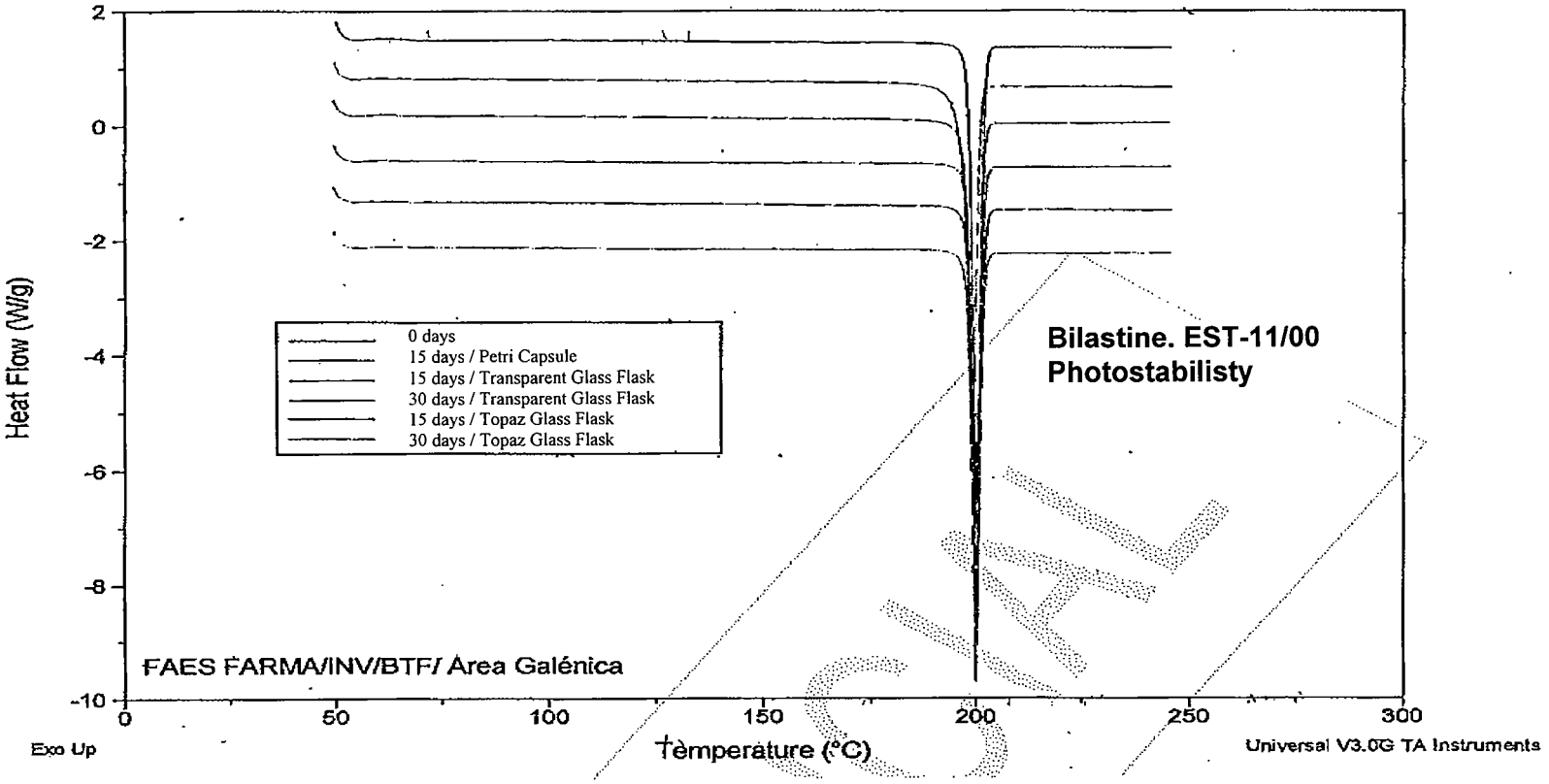

Figure 1. Batch 3600J25 (Polymorph 1) kept in photostability chamber during 30 days (EST-11/00)

ATTACHMENT G

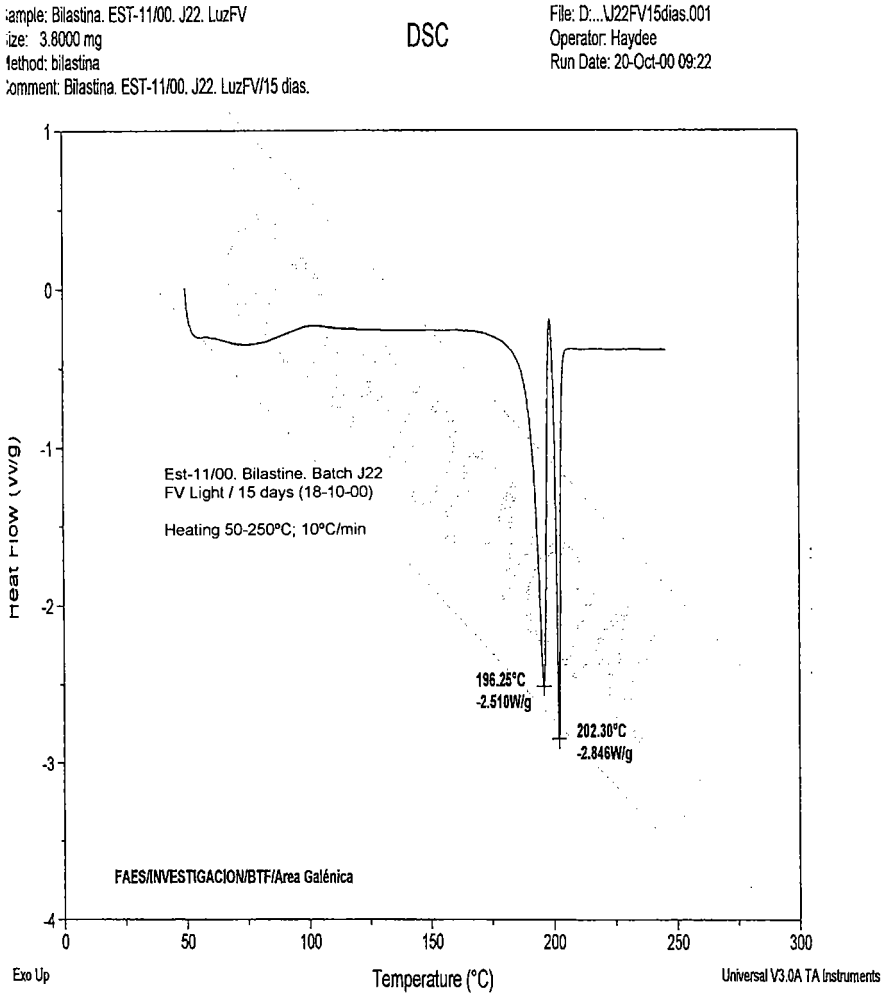

Figure 2. Batch J22 (Mixture Polymorphs 2+3) kept in photostability chamber during 15 days (EST-11/00)

ATTACHMENT H

Table 5: Summary of stability studies in stress, accelerated, intermediate and long term conditions

Study code	Batch (Date of manuf./Size)	Packaging	Type of study	Conditions	Duration (months)
EST-10/00	3600J25 (Sep 00 / 0.5 kg)	Glass bottle w bakelite screw on cap	Stress	60°C/40 %RH	3
			Stress	50°C/50 %RH	6
			Accelerated	40°C/75 %RH	12
			Long term	25°C/60 %RH	24
		PP bottle w plastic screw on cap	Long term	25°C/60 %RH	24
EST-08/01	7RR/1B (May 01 / 5.6 kg) 7RR/2B (Jun 01 / 6.4 kg) 7RR/3B (Jun 01 / 6.4 kg)	Glass bottle w bakelite screw on cap	Stress	50°C	6
			Accelerated	40°C/75 %RH	12
			Long term	25°C/60 %RH	36
		PP bottle w plastic screw on cap	Long term	25°C/60 %RH	36
EST-02/03	4002J40 (Oct 02 / 17.7 kg)	Glass bottle w plastic screw on cap	Stress	60°	12
			Stress	50°	12
			Accelerated	40°C/75 %RH	24
			Intermediate	30°C/65 %RH	36
EST-03/03	4202J41-2 (Oct 02 / 17.1 kg)	Glass bottle w plastic screw on cap	Stress	60°	12
			Stress	50°	12
			Accelerated	40°C/75 %RH	24
			Intermediate	30°C/65 %RH	36
EST-04/03	4602J44-3 (Nov 02 / 16.3 kg)	Glass bottle w plastic screw on cap	Stress	60°	12
			Stress	50°	12
			Accelerated	40°C/75 %RH	24
			Intermediate	30°C/65 %RH	36
EST-04/04	48216-01 (Jul 04 / 15.0 kg)	Glass bottle w bakelite screw on cap	Stress	60°C	12
			Stress	50°C	12
			Stress	25°C/80-90 %RH	3
		PE bottle w plastic screw on cap	Stress	25°C/80-90 %RH	3
		Glass bottle w bakelite screw on cap	Accelerated	40°C/75 %RH	12
		PE bottle w plastic screw on cap	Accelerated	40°C/75 %RH	12
EST-06/04		Glass bottle w bakelite screw on cap	Long term	25°C/60 %RH	36
		PE bottle w plastic screw on cap	Long term	25°C/60 %RH	36

ATTACHMENT I

Table 6: Study EST- 02/03: Stability data for batch 4002J40 (Batch size: 17.7 kg; Date of manuf. Oct 02; FAES FARMA)

Type of Study	Conditions Container	Storage time	Appearance	Assay (%)	Moisture (%)	Impurities (%)						DSC	
						F-98226-BM	F-97614-BM	F-90021-RR	F-97617-BM	UID	Total (ID+UID)	Polymorph	Onset Temp. (°C)
	Specifications		White or off-white powder	97.5-101.5 %	≤0.5 %	≤0.7 %	≤0.2 %	≤0.4 %	≤0.2 %	≤0.1 %	≤1.5 %	Corresponds to polymorph I	
	-	Initial	Conforms	99.0	0.1	0.38	<QL	0.21	ND	<QL	0.59	I	199.19
Stress	60°C Glass bottle w plastic screw on cap	1 month	Conforms	99.5	0.2	0.38	ND	0.22	ND	<QL	0.60	I	199.19
		2 months	Conforms	100.0	0.1	0.39	ND	0.22	ND	<QL	0.61	I	199.21
		3 months	Conforms	99.1	0.2	0.38	ND	0.22	ND	<QL	0.60	I	199.11
		6 months	Conforms	97.9	0.2	0.40	ND	0.22	ND	<QL	0.62	I	199.03
		9 months	Conforms	99.4	0.1	0.38	ND	0.21	ND	<QL	0.59	I	199.13
		1 year	Conforms	99.9	0.1	0.38	ND	0.21	ND	<QL	0.59	I	199.17
	50°C Glass bottle w plastic screw on cap	1 month	Conforms	98.9	0.2	0.38	ND	0,22	ND	<QL	0.60	I	199.21
		2 months	Conforms	99.9	0.1	0.38	ND	0,22	ND	<QL	0.60	I	199.16
		3 months	Conforms	98.8	0.2	0.38	ND	0,22	ND	<QL	0.60	I	199.21
		6 months	Conforms	100.0	0.2	0.38	ND	0,21	ND	<QL	0.59	I	199.21
		9 months	Conforms	99.4	0.1	0.38	ND	0.21	ND	<QL	0.59	I	199.13
		1 year	Conforms	99.6	0.1	0.38	ND	0.21	ND	<QL	0.59	I	199.15
Accelerated	40°C/75 % RH Glass bottle w plastic screw on cap	1 month	Conforms	98.8	0.2	0.38	ND	0.22	ND	<QL	0.60	I	199.15
		2 months	Conforms	99.8	0.1	0.38	ND	0.22	ND	<QL	0.60	I	199.19
		3 months	Conforms	99.1	0.2	0.38	ND	0.22	ND	<QL	0.60	I	199.22
		6 months	Conforms	99.7	0.2	0.38	ND	0.21	ND	<QL	0.59	I	199.20
		9 months	Conforms	100.2	0.2	0.38	ND	0.21	ND	<QL	0.59	I	199.13
		1 year	Conforms	100.1	0.2	0.38	ND	0.21	ND	<QL	0.59	I	199.19
		1.5 years	Conforms	98.3	0.2	0.38	ND	0.21	ND	<QL	0.59	I	199.18
		2 years	Conforms	99.3	0.1	0.38	ND	0.20	ND	<QL	0.58	I	199.08
Intermmediate	30°C65 % RH Glass bottle w plastic screw on cap	3 months	Conforms	98.4	0.2	0.38	ND	0.22	ND	<QL	0.60	I	199.14
		6 months	Conforms	99.5	0.2	0.38	ND	0.21	ND	<QL	0.59	I	199.21
		9 months	Conforms	99.4	0.2	0.38	ND	0.21	ND	<QL	0.59	I	199.12
		1 year	Conforms	100.1	0.1	0.38	ND	0.21	ND	<QL	0.59	I	199.18
		1.5 years	Conforms	100.4	0.2	0.38	ND	0.21	ND	<QL	0.59	I	199.25
		2 years	Conforms	99.8	0.1	0.38	ND	0.20	ND	<QL	0.58	I	199.13
		2.5 years	Conforms	99.6	0.2	0.38	ND	0.22	ND	<QL	0.60	I	199.20
		3 years	Conforms	99.2	0.1	0.38	ND	0.21	ND	<QL	0.59	I	199.18